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PRODUCTION AND PROPERTIES OF 2,3-BUTANEDIOL

XVI. DENSITY, OPTICAL ROTATORY POWER, AND REFRACTION OF AQUEOUS 2,3-BUTANEDIOL SOLUTIONS[1]

BY K. A. CLENDENNING[2]

Abstract

Addition of water to the *levo*- and *meso*-isomers of 2,3-butanediol increases the specific gravity to a maximum at 50 to 60% diol, beyond which it is gradually reduced. Contraction on mixing is strongly influenced by temperature and is slightly greater with the *levo*- than with the *meso*-isomer. The coefficient of thermal expansion for the *levo*-isomer is higher than that of the *meso*-form. Water exerts a pronounced influence on the specific rotation value of the *levo*-isomer, reducing it from −13° (anhydrous) to approximately −9° for solutions containing 40 to 70% water; on further dilution, the specific rotation value rises. With increase in temperature, the optical rotatory power of the anhydrous *levo*-isomer is reduced, whereas that of 30 to 90% aqueous solutions is increased. Refractive index data are provided for aqueous *meso*-2,3-butanediol solutions at 25° C. and for aqueous *levo*-2,3-butanediol solutions at 20°, 25°, 30°, and 35° C. From several lines of evidence it is concluded that the hydration tendencies of the two isomers are approximately equivalent.

Introduction

Aqueous solutions of *meso*- and *levo*-2,3-butanediol exhibit remarkable differences in freezing point at identical glycol concentrations (2, 4). Corresponding dissimilarities evidently have yet to be reported for aqueous solutions of the diastereoisomers of other compounds. Ward, Pettijohn, Lockwood, and Coghill (11) and Knowlton, Schieltz, and Macmillan (4) have attributed these well established differences between the 2,3-butanediols to hydrate formation by the *meso*- and lack of hydrate formation by the *levo*-isomer. The ability of the *meso*-form to yield a hydrate that crystallizes above the freezing point of water provides conclusive evidence for hydration in its aqueous solutions. The *levo*-isomer possesses the same functional groupings, however, and there is no immediately apparent reason for supposing that it differs greatly from the *meso*-isomer in its affinity for water. Apart from its failure to yield an isolable hydrate, the existing experimental evidence on the *levo*-isomer indicates that its aqueous solutions are characterized by hydration. This isomer is strongly hygroscopic and exhibits considerable heat of solution on mixing with water. The density of its aqueous solutions exceeds those of

[1] *Manuscript received May 21, 1946.*

Contribution from the Division of Applied Biology, National Research Laboratories, Ottawa. Issued as Paper No. 43 on Industrial Utilization of Wastes and Surpluses and as N.R.C. No. 1440.

[2] *Biochemist, Industrial Utilization Investigations.*

either pure component over a wide range of concentrations (7). Freezing point lowering by the *levo*-isomer consistently exceeds the values calculated from the Raoult–van't Hoff equation. Aqueous solutions of the *levo*- and *meso*-isomers also exhibit a striking similarity in their absolute viscosity/diol concentration relations (2). If hydration occurs in aqueous solutions of either isomer, their differences in freezing point require reinterpretation.

Ward *et al.* (11) and Neish (6) reported specific rotation values above $-13°$ for pure *levo*-2,3-butanediol. From the results of an intensive study, Neish (6) concluded that the 2,3-butanediol formed in the *Aerobacillus polymyxa* fermentation consists entirely of the *levo*-isomer. Butanediol samples obtained with *Aerobacillus* often show low polarization values (2, 4). Knowlton *et al.* (4) claimed that such samples were contaminated with the *meso*-isomer, presumably formed in the fermentation. To clarify this point, information appeared desirable on the effects of temperature and of traces of water and esterified butanediol on the "specific" rotation value.

When plotted against diol concentration, existing data on the refractivity of aqueous *levo*- and *meso*-2,3-butanediol solutions show serious irregularities (4, 8). The magnitude of the effects of temperature on this property also had not been established.

The situation as outlined above prompted the present study, which is concerned chiefly with the effects of diol concentration and temperature on the specific gravity, optical rotatory power, and refractivity of aqueous 2,3-butanediol solutions.

Materials and Methods

The 2,3-butanediols were prepared from fermented wheat mashes by methods that have already been described in detail (6, 10) and were redistilled at 40 to 45 mm. of mercury immediately before use. The diol obtained with *Aerobacter aerogenes* ($[\alpha]_D^{20} = +0.8°$) will be referred to as the *meso*-isomer, it being understood that the usual 5 to 10% of *dextro*-isomer was present. Solutions were prepared by accurate weighing, and, unless otherwise stated, the data are expressed on a weight percentage basis.

The diacetate of the *levo*-isomer was prepared by mixing 117 gm. acetic anhydride, 45 gm. *levo*-2,3-butanediol, and one drop of concentrated sulphuric acid, and allowing to stand one day at room temperature. The solution was distilled at 5 to 10 mm. of mercury, and the fraction boiling at 76 to 78° C. was collected. The crude diacetate was purified by crystallization from petroleum ether, yield 45 gm.

Specific gravity was determined by the conventional pycnometer method with minor modifications (3), temperature control being within $\pm 0.02°$ C. Before beginning the present series of estimations, reproducibility of the technique was tested against distilled water. Ten successive specific gravity measurements agreed to the nearest fifth decimal point, the standard deviation for the weight of the filled pycnometer being ± 0.0005 gm. Since other sources of error could not be entirely excluded, the data for diol solutions were

calculated to the nearest fourth decimal point. Corrections were not introduced for air buoyancy because of their uniformly low magnitude.

Isothermal contraction in volume on mixing 2,3-butanediol with water was determined by calculating the volume of the components before and after mixing at each temperature, expressing contraction as millilitres per 100 ml. initial volume (1, p. 57). Thermal expansion was determined from the equation $d_4^{20}/d_4^{40} = 1 + 20\ \alpha$, which is an adaptation of the expression $V_t = V_o\ (1 + \alpha\ t)$.

The refractive index values were obtained with a Bausch and Lomb Abbé refractometer. The polarimetric measurements were made with an Adam Hilger polarimeter, and a General Electric sodium vapour lamp was employed as light source. The liquids were brought to bath temperature before they were placed in water-jacketed polarimeter tubes. During the course of the refraction and optical rotatory power measurements, temperature control was maintained within $\pm$ 0.1° C.

Results

Specific Gravity

With increasing diol content, the specific gravity of aqueous 2,3-butanediol solutions rises to a maximum at 50 to 60% diol, and then declines gradually to the values of the anhydrous isomers (Figs. 1, 2). The similarity of the

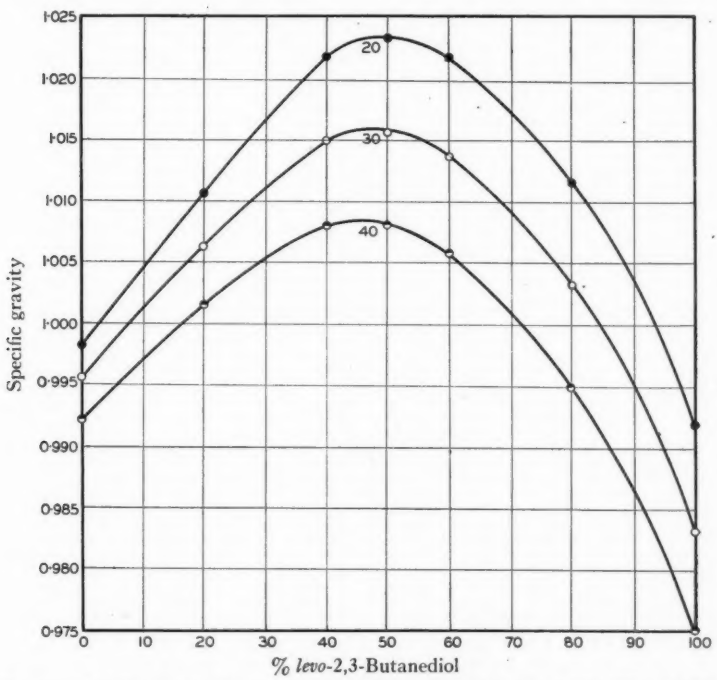

FIG. 1. *Specific gravity of aqueous levo-2,3-butanediol solutions at 20°, 30°, and 40° C.*

changes in specific gravity resulting from the effects of concentration and temperature indicates that the affinities of the *levo-* and *meso-*isomers for water are approximately equivalent.

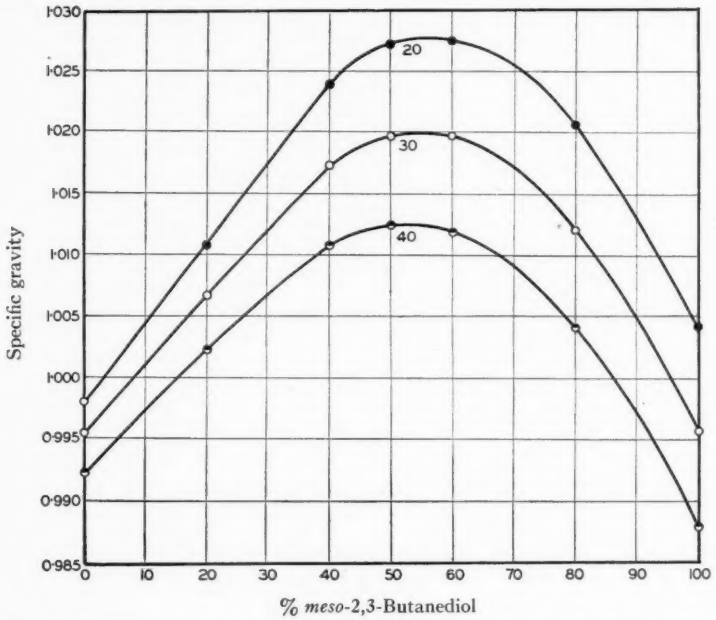

FIG. 2. *Specific gravity of aqueous meso-2,3-butanediol solutions at 20°, 30°, and 40° C.*

Contraction on Mixing

Tables I and II provide derived data on the contraction in volume that occurs on mixing 2,3-butanediol isomers with water in different proportions at 20°, 30°, and 40° C. Slightly less contraction occurs on mixing water with the *meso-* as compared with the *levo-*isomer. The cause of this difference

TABLE I

CONTRACTION IN VOLUME ON MIXING *levo*-2,3-BUTANEDIOL WITH WATER AT DIFFERENT TEMPERATURES

Wt. of glycol, gm.	Wt. of water, gm.	Contraction in ml. per 100 ml. initial volume		
		20° C.	30° C.	40° C.
9.9990	40.1195	1.35	1.27	1.26
20.0014	30.0580	2.59	2.38	2.26
25.0153	25.1259	2.66	2.57	2.43
30.0467	20.1089	2.70	2.50	2.37
40.0060	10.0074	1.83	1.72	1.66

TABLE II

CONTRACTION IN VOLUME ON MIXING *meso*-2,3-BUTANEDIOL WITH WATER AT DIFFERENT TEMPERATURES

Wt. of glycol, gm.	Wt. of water, gm.	Contraction in ml. per 100 ml. initial volume		
		20° C.	30° C.	40° C.
10.0141	40.0192	1.14	1.10	1.10
19.9990	30.2180	2.28	2.11	2.02
25.0276	25.0238	2.51	2.31	2.18
30.0111	20.2621	2.49	2.31	2.21
40.0242	10.0277	1.74	1.60	1.52

evidently lies in the more compact structure or closer association of the *meso*-isomer in the anhydrous state. Less contraction occurs on mixing butanediol and water at high than at low temperatures, temperature having greatest effect at diol concentrations of 40 to 60%. Within the investigated temperature range, maximum contraction was consistently observed at butanediol concentrations of 50 to 60%.

Thermal Expansion

The coefficient of thermal expansion for 2,3-butanediol solutions increases as the water content is reduced (Table III). With rising temperature the

TABLE III

THERMAL EXPANSION OF AQUEOUS 2,3-BUTANEDIOL SOLUTIONS BETWEEN 20° AND 40° C.

Diol, %	$\alpha \times 10^3$*	
	levo	*meso*
0	0.30	0.30
20	0.45	0.42
40	0.77	0.65
50	0.75	0.72
60	0.79	0.76
80	0.83	0.81
100	0.85	0.82

* *Calculated from the equation* $d_4^{20}/d_4^{40} = 1 + 20\alpha$

meso-form undergoes slightly less expansion than the *levo*-form, both in the presence and absence of water. Since molecular movement in the aqueous solutions is impeded to a slightly greater extent by the *meso*- as opposed to the *levo*-configuration it would appear that small but real differences exist between the isomers in their degree of affinity for water.

Optical Rotatory Power

The polarization value of optically active 2,3-butanediol isomers is the most commonly used criterion of their relative purity. On the assumption

that impurities reduce the specific rotation, the purest sample should have the highest specific rotation value. The highest value for the *levo*-isomer ($[\alpha]_D^{26} = -13.34°$) was reported by Neish (6) and the corresponding 1 dm. polarization value, uncorrected for density, was $-13.19°$.

Samples of *levo*-2,3-butanediol often show polarization values considerably less than $-13°$ although their boiling points, refractive indices, and densities closely approximate those of samples having polarization values above $-13°$. Since acetic acid is produced in considerable quantities in the *Aerobacillus polymyxa* fermentation, the mono- and diacetates are apt to be present as impurities in the recovered diol. The diacetate of the *levo*-form showed the following properties: n_D^{25} 1.4132; d_4^{20} 1.029; $[\alpha]_D^{28}$ + 13.65°. The presence of this compound as an impurity would accordingly have considerable effect on the polarization value although causing little change in the refractive index

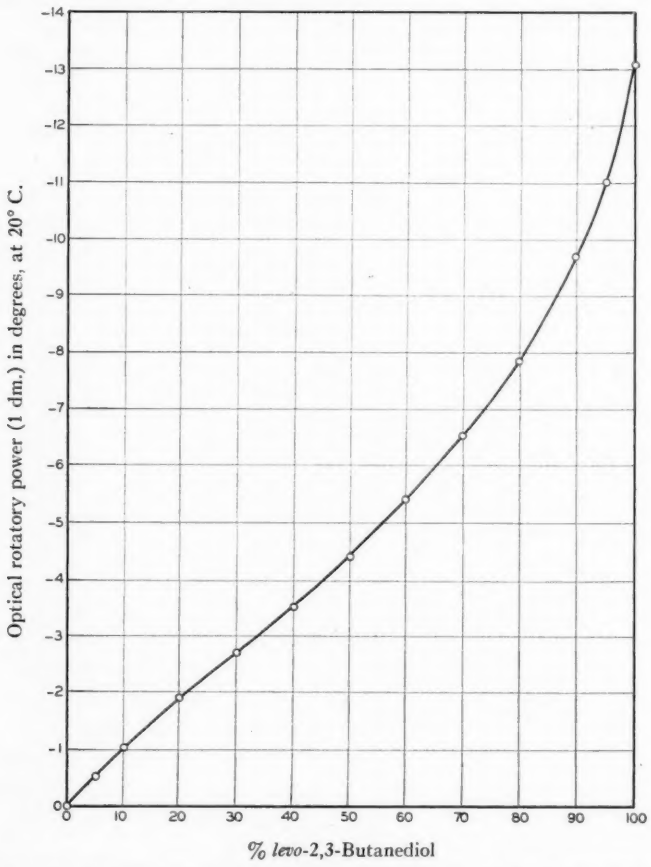

FIG. 3. *Optical rotatory power of aqueous levo-2,3-butanediol solutions at 20° C.*

and density. The same is believed to apply to the monoacetate, although its effect on the polarization value undoubtedly would be less pronounced.

Since 2,3-butanediols are strongly hygroscopic, the effect of water on the rotatory power of the *levo*-isomer warrants consideration as a possible cause of low polarization values. Fig. 3 shows that the polarization value is reduced very markedly by small amounts of water, the solvent influence being considerably greater than if water were merely serving as an inert diluent. Such an effect suggests polar association of water and *levo*-2,3-butanediol as the most probable cause. Since rising temperature leads to dissociation of higher order compounds, the effects of water on the optical rotatory power of *levo*-2,3-butanediol should be strongly influenced by changes in temperature, high temperatures leading to diminished hydration and consequent reduction of the effects of water on the polarization value.

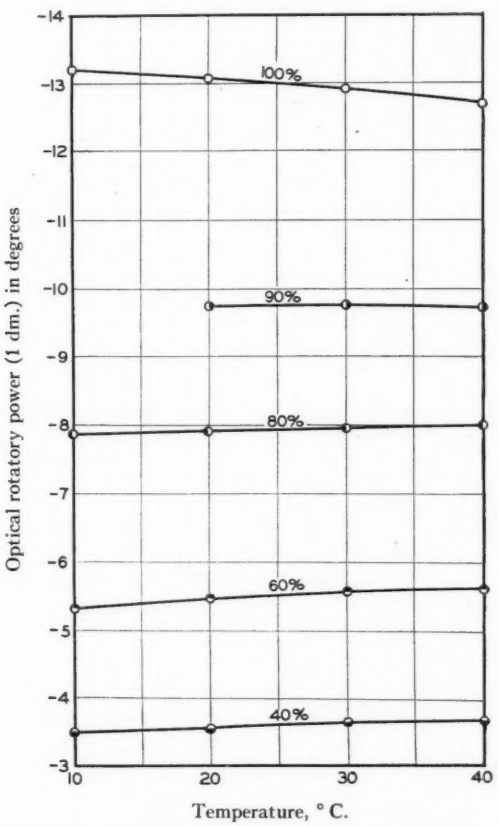

FIG. 4. *Influence of temperature on the optical rotatory power of levo-2,3-butanediol and of its aqueous solutions at concentrations of 40 to 90%.*

Fig. 4 shows that the optical rotatory power of anhydrous *levo*-2,3-butanediol is reduced by rising temperature. In the presence of 20% or more of water, the dominant effect of rising temperature on the polarization value arises from hydrate dissociation; in the presence of 10% of water, the opposing effects of temperature are almost exactly balanced. As might be anticipated from the specific gravity data, the 60% solution shows a larger increase in polarization value with rising temperature than either the 80 or 40% solutions.

In Fig. 5, the optical rotation data are presented as specific rotation, calculated from the conventional formula $[\alpha] = \frac{\alpha}{l \epsilon \delta}$, where α = observed rotation in degrees, l = length of column in decimetres, δ = density of the liquid, ϵ = fraction by weight of the optically active compound. At 20° C.

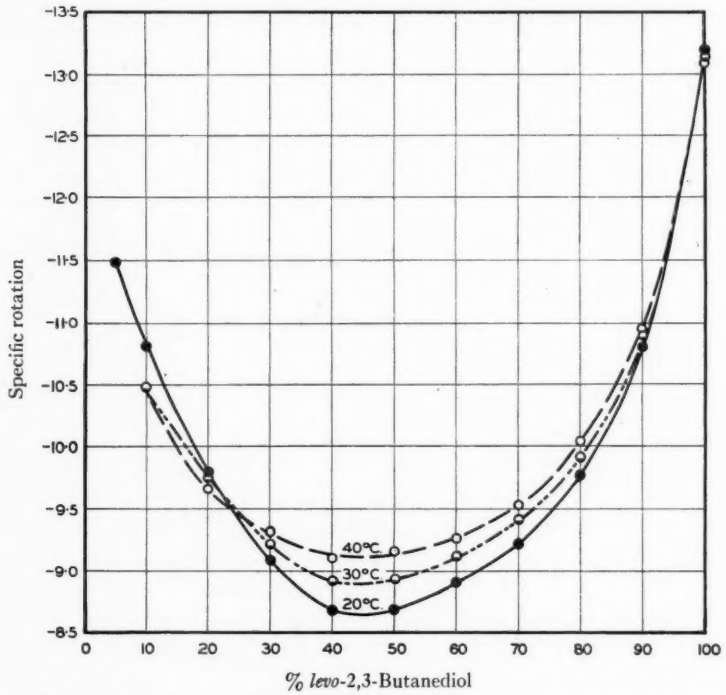

FIG. 5. *Effects of concentration and temperature on the specific rotatory power of levo-2,3-butanediol in aqueous solution.*

the specific rotation value is reduced from −13° for the anhydrous liquid to approximately −9° for solutions containing 30 to 60% diol. With diol concentrations of 30 to 90%, the specific rotation values are consistently higher at 30° and 40° C. than at 20° C. On dilution to concentrations of 20% diol and less, the specific rotation value rises. Evidently as the butanediol

molecules become widely separated, association of water with water becomes increasingly important, with consequent reduction in the effect of the solvent on the optically active solute.

Refractive Index

The refractive indices of aqueous solutions of the *levo-* and *meso*-isomers of 2,3-butanediol presented in Fig. 6 show general conformity with the data presented by Othmer, Shlechter, and Koszalka (8) and Knowlton, Schieltz,

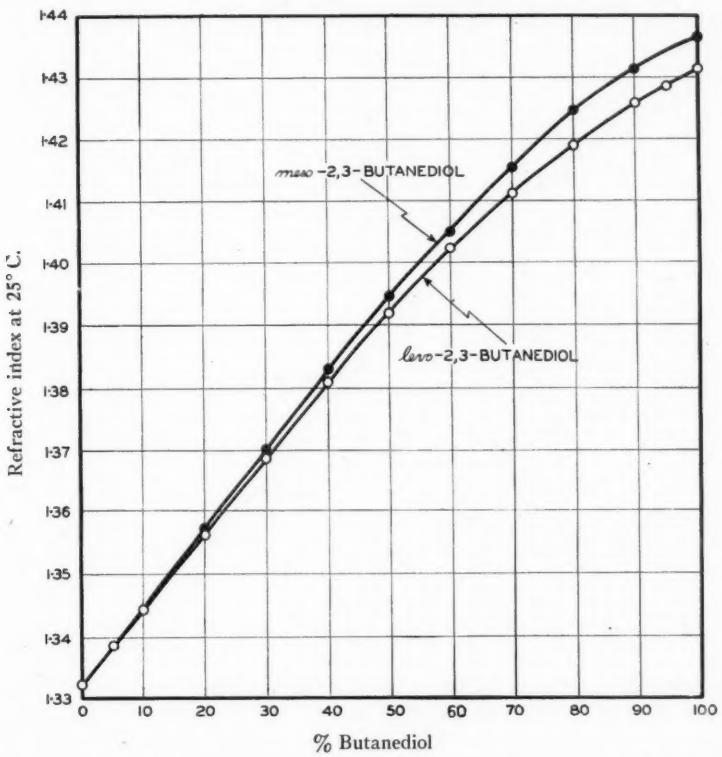

FIG. 6. *Refractive indices of aqueous solutions of meso- and levo-2,3-butanediol at 25° C.*

and Macmillan (4) respectively. The molar refractivity, calculated from the expression $\frac{n^2 - 1}{n^2 + 2} \cdot \frac{M}{d}$, is 23.59 for the *meso-* (n_D^{25} 1.4366, d_4^{25} 0.9998) and 23.62 for the *levo*-isomer (n_D^{25} 1.4308, d_4^{25} 0.9873). The value calculated from tables of refraction equivalents is 23·56 (6).

The data of Table IV, which were obtained with a relatively impure sample of *levo*-2,3-butanediol ($[\alpha]_D^{20} = -12.92$), are included for purposes of reference in practical control work. Sensitivity of the refractive index values to

TABLE IV

REFRACTIVE INDICES OF AQUEOUS *levo*-2,3-BUTANEDIOL SOLUTIONS AT DIFFERENT TEMPERATURES

Diol, %	Temp., ° C.			
	20	25	30	35
0	1.3330	1.3325	1.3319	1.3312
10.0	1.3450	1.3445	1.3437	1.3429
19.9	1.3574	1.3566	1.3557	1.3549
29.9	1.3700	1.3689	1.3677	1.3666
39.9	1.3820	1.3807	1.3793	1.3779
49.9	1.3930	1.3915	1.3900	1.3885
59.6	1.4027	1.4012	1.3997	1.3982
70.0	1.4115	1.4098	1.4082	1.4065
79.7	1.4197	1.4180	1.4162	1.4146
89.7	1.4264	1.4247	1.4229	1.4212
99.5	1.4322	1.4302	1.4283	1.4264

temperature change is strongly influenced by diol concentration. The data of Table IV indicate that the refractive index values are not changed sufficiently by 0.5° variation in temperature to exceed the error of observation ($\pm$ 0.0003) with the Abbé refractometer.

Discussion

The specific gravity and specific rotation data presented above are considered to establish the importance of hydration in aqueous solutions of *levo*- as well as *meso*-2,3-butanediol. In seeking an alternative explanation to that offered by Ward *et al.* (11) for the marked differences in their freezing points, attention should be drawn to the basic distinction between crystalline and amorphous states: crystals are characterized by oriented lattice structures, amorphous states by random arrangement. In the absence of water, the *meso*-isomer freezes or forms oriented lattice structures at a higher temperature than the *levo*-isomer. Both isomers undergo hydration in aqueous solution, and the configurational influence is again responsible for the decidedly greater difference in freezing point that is exhibited in this state: upon hydration, the difference in orientation tendency shown by the anhydrous isomers is greatly magnified.

The present demonstration of the effect of water on the specific rotatory power of *levo*-2,3-butanediol represents additional information on a relatively obscure aspect of solvent action. Landolt (5) reported that water had a remarkable and puzzling influence on the specific rotation values of ethyl tartrate and nicotine: on diluting ethyl tartrate with water to a concentration of 10%, the specific rotation value rose progressively from + 8.5° to +26.2°; similar treatment of nicotine reduced its specific rotation from −162° to −76°. Patterson (9) showed that the solvent effect observed with ethyl tartrate was progressively reduced on replacing water with methanol, ethanol, and pro-

panol, respectively. A similar reduction of the solvent effect was observed by Winther (12, 13) in corresponding studies of nicotine solutions. Solvents representing a graded polarity series, such as were used by these investigators, presumably would cause a similar modification of the specific rotation value of *levo*-2,3-butanediol. Since its molecules are of simple structure and have polar substituents on the asymmetric carbon atoms, *levo*-2,3-butanediol should be particularly useful in further studies of solvent influences.

Acknowledgments

The author wishes to express his indebtedness to Mr. F. J. Macdonald, who supplied the samples of butanediol, and to Mr. D. E. Wright, who prepared the figures and assisted with the physical measurements.

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THE DETECTION OF ETHYL*BIS*(β-CHLOROETHYL)AMINE[1]

R. P. GRAHAM[2] AND K. A. BURKE[3]

Abstract

Aqueous solutions of ethyl*bis*(β-chloroethyl)amine and Reinecke salt react to yield a pink crystalline precipitate. The sensitivity of the test depends on a number of factors, but, under suitable conditions, Reinecke salt will detect less than 5 p.p.m. of this amine in aqueous solution.

Introduction

Ethyl*bis*(β-chloroethyl)amine, $C_2H_5N(CH_2CH_2Cl)_2$, is closely related structurally to substances that have an irritating (trichlorotriethylamine (16)) or vesicant (methyl*bis*(β-chloroethyl)amine (9)) action on the skin.* It does not appear to have been noted that Reinecke salt (5, pp. 555-556), $NH_4[Cr(NH_3)_2(SCN)_4] \cdot H_2O$, may be used for the detection of ethyl*bis*(β-chloroethyl)amine or water contaminated with this amine. It is well known, however, that Reinecke salt or the corresponding acid serves as a precipitant for many organic bases (1, 2, 3, 10, 20) and for a number of amino acids (4, 7, 15, 19). Reineckates may be used to aid in the characterization of certain bases (8, 17), and are of service in effecting a number of isolations and separations (11, 12, 13, 14, 19, 20, 21). It was in the form of reineckates, for example, that the antibiotically active bases streptomycin and streptothricin were first obtained in the form of crystalline salts (6).

Experimental

It was found that when ethyl*bis*(β-chloroethyl)amine is added to an aqueous solution of Reinecke salt, a precipitate is formed (unless the concentrations of reactants are too low).

Nature of Precipitate

The precipitate is composed of tiny pink lustrous crystals. An attempt was made to determine the melting point of the crystals, but it was found that they

[1] *Manuscript received May 21, 1946.*

Contribution from the Department of Chemistry, McMaster University, Hamilton, Ont., with financial assistance from the National Research Council of Canada. The work reported in this paper is largely drawn from an N.R.C. report of restricted circulation, dated November 15, 1944.

[2] *Assistant Professor of Chemistry.*

[3] *Formerly Graduate Student; at present, Junior Research Chemist, Division of Physics and Electrical Engineering, National Research Council, Ottawa.*

* *Since this paper was written, the pathologic effects of ethylbis(β-chloroethyl)amine (a vesicant of the "nitrogen mustard" family) have been published (Graef, et al., Federation Proc., Part II, Vol. 5, pp. 221-2, Feb. 1946). Attention was drawn to the peace-time biochemical and medical interest in the nitrogen mustards at the meetings of the Federation of American Societies for Experimental Biology and of the American Association for Cancer Research, held in Atlantic City, N.J., in March, 1946, and at the 109th meeting of the American Chemical Society held at Atlantic City, N.J., in April, 1946. The biological actions of nitrogen mustards and their possible therapeutic applications in the treatment of Hodgkin's and other diseases have recently been discussed by Gilman and Philips (Science, 103 : 409-415. (April 5, 1946)).*

PLATE I

FIG. 1. *Electron microscope pictures of reineckate crystals (obtained through the courtesy of the Radiology Section of the National Research Council of Canada). Magnification: 400-600.*

decomposed on heating; darkening and shrinking of the crystals was observed at 132° C. (corr.) (the dark red-brown decomposition product melted below 187° C.).

Photographic studies have indicated that the shape of the crystals depends to some extent on the conditions of precipitation, viz., age of reactant solutions, and absolute and relative concentrations of amine and Reinecke salt, but in all cases the crystals are definitely elongated. With a given set of conditions, more than one type of crystal may be obtained; in Fig. 1 are shown several shapes of crystals formed by the interaction of one-day-old solutions of amine and Reinecke salt. Under other conditions, elongated crystals with distinctly serrate edges may be obtained.

Relation of Precipitation to Age of Amine Solution

A number of experiments were carried out in which the amount of reineckate precipitate was studied as a function of the age of an aqueous solution of the amine. The precipitations were carried out in a graduated conical centrifuge tube in which the volume of precipitate was read after centrifugation. The volume of precipitate so obtained depends not only on the age of the amine solution and on the time and the rate of centrifugation, but also on the time allowed for interaction before centrifugation and on the age of the Reinecke salt solution (Reinecke salt is not stable in aqueous solution (5, pp. 555-556)). With the adoption of a fixed technique of experimentation, it was found possible to obtain good checks in following the variation in the amount of precipitate produced as the amine solution aged (at room temperature). Fig. 2 shows a plot of the results obtained over a 25 hr. period (1% aqueous

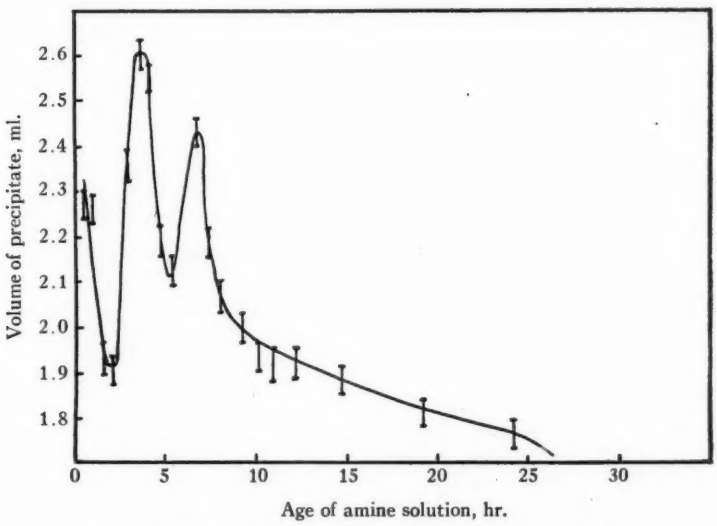

FIG. 2. *Variation in reineckate precipitation with age of amine solution.*

solutions of the amine and Reinecke salt were mixed so that the resultant concentrations, before interaction, were 2.00×10^{-2} ml. of amine and and 8.00×10^{-2} gm. of salt in 10.00 ml. of solution).

In other similar experiments, which were carried out under slightly different conditions, the presence of maxima in the curve during the first 11 hr. in the life of the amine solution was confirmed, although the position of the maxima relative to the time scale was observed to depend, like the volume of precipitate recorded, on the details of the experimental technique. As the amine solution ages beyond 25 hr. the yield of reineckate precipitate decreases, but at a decreasing rate; tests were carried out over a period of 1350 hr., but the amount of precipitate was essentially constant (0.4 ml.) after about 600 hr.

It may be mentioned that in these and other experiments, it was found that an apparatus similar to the one described by Schneider (18) was very useful for filling and delivering the micropipette employed for measuring the liquid amine.

Use of Reinecke Salt for Detection of Amine

The sensitivity of this test for the detection of ethyl*bis*(β-chloroethyl)-amine in aqueous solution was determined, using aqueous amine solutions of various concentrations, by noting the lowest concentration of amine that would yield a detectable amount of reineckate precipitate under fixed conditions of experimentation. The procedure employed was as follows.

From a microburette, 2.00 ml. of dilute amine solution was run into a 15 ml. conical graduated (to 0.1 ml.) centrifuge tube and 8.00 ml. of 1% aqueous Reinecke salt solution (centrifuged or filtered free of any sediment just prior to use) rapidly added; the resultant solution was allowed to stand for one minute during which time it was stirred, and then it was centrifuged under reproducible conditions. All determinations were carried out in duplicate; good checks were obtained. The "limit of detection" in Table I refers to the concentration of amine in solution before the fivefold dilution with Reinecke salt solution.

TABLE I

SENSITIVITY OF REINECKATE TEST

Reinecke solution	Amine solution	Limit of detection
Freshly prepared	Aged* 10 days	Between 5 and 10 p.p.m.
Aged* 25 hr.	Aged* 10 days	Between 1 and 5 p.p.m.
Aged* 27 hr.	Freshly prepared	Between 1 and 5 p.p.m.

* *At room temperature.*

The test is appreciably less sensitive if one depends on visual detection of the amine reineckate precipitate previous to centrifugation. The very tiny lustrous crystals formed on the addition of the Reinecke salt solution to a freshly prepared (or one-day-old) solution of the amine containing the latter

at a concentration of one part in 20,000 are, however, evident without centrifugation within a minute after the solutions are mixed.

Other Possible Precipitants for Amine

Aqueous solutions of a number of complex chromium compounds related to Reinecke salt, viz., $(NH_4)_3[Cr(SCN)_6]$, $K_3[Cr(SCN)_6]$, $Cr(NH_3)_3(SCN)_3$, $[Cr(NH_3)_4(SCN)_2]$ (SCN), and $[Cr(NH_3)_5(SCN)]$ $(SCN)_2$, were tested for their reactivity toward ethyl*bis*(β-chloroethyl)amine. On the addition of liquid amine to solutions of these compounds it was found that, although in most cases spectrophotometric examination of the solutions gave some evidence of reaction, distinct precipitates were produced only with the two hexathiocyanato compounds. These precipitates were light blue in colour, and not nearly as voluminous as the precipitate produced by Reinecke salt under the same conditions of experimentation. The same two chromiates will also react, at suitable concentrations, with aged aqueous solutions of the amine to yield precipitates similar or identical to those produced by dissolving liquid amine in solutions of the complex compounds. Ammonium and potassium hexathiocyanato chromiates are much inferior to Reinecke salt for the purpose of detecting the amine; sensitivity tests of the type described above (but using 12-day-old amine) showed the limit of detection to be between 0.1 and 1%.

Discussion

The experiments in which photographs (Fig. 1) were taken indicate that it is probable that the hydrolysis of ethyl*bis*(β-chloroethyl)amine gives rise to several products, more than one of which react with an aqueous solution of Reinecke salt. The experiments with an ageing solution of the amine furnish further evidence that the mechanism of the hydrolysis of this amine is a complicated one, and make it evident that Reinecke salt cannot be conveniently employed for the quantitative estimation of ethyl*bis*(β-chloroethyl)-amine when the latter is in fresh aqueous solution.

The reaction of a solution of Reinecke salt with the amine forms the basis of a qualitative test for the detection of the latter—a test that will detect, under controlled experimental conditions, less than 5 p.p.m. of the amine in aqueous solution. Reinecke salt is more suitable for this test than a number of complex chromium compounds structurally related to it.

Acknowledgments

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LIQUID-VAPOUR EQUILIBRIUM FOR THE SYSTEM HYDROGEN-CYANIDE–CYANOGEN-CHLORIDE[1]

By A. R. Gordon[2] and G. C. Benson[3]

Abstract

The binary liquid–vapour equilibrium for the system hydrogen-cyanide–cyanogen-chloride has been investigated at 15° C. The equilibrium liquid–vapour compositions were determined by slow isothermal distillation and the vapour pressures by mercury manometer. Analysis of the phases was by density, independent measurements having fixed the density–liquid composition curve. It is shown how true equilibrium compositions may be obtained from the measured (average) compositions of the distillates.

The measurements reported here were undertaken to study the vapour-liquid equilibrium for the system hydrogen-cyanide–cyanogen-chloride. The results, although not susceptible of analysis by means of the Gibbs–Duhem equation as were those for the systems ethanol–acetone (4) and ethanol–ethyl-ether (5), are nevertheless of interest. Moreover, the technique employed—slow isothermal distillation—is so simple, and of such wide applicability that we believe attention should be called to it, especially since certain corrections may now be made that largely remove the difficulty of interpreting conventional distillation data in terms of equilibrium concentrations.

Experimental

The apparatus is illustrated in Fig. 1, and somewhat resembles that of Roberts and Mayer (9); the principal differences are that Roberts and Mayer

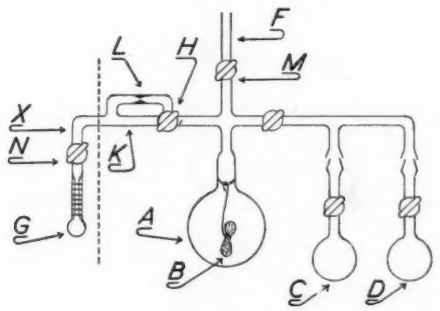

Fig. 1.

used mercury U's in place of stopcocks, and that their distillations involved the removal of only about 1% of the liquid phase as compared with the 5 to

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7% used in this research; the practical advantage of being able to use a larger distillate fraction is obvious. The small flask *A* of approximately 40 cc. capacity contains the liquid phase; suspended by platinum in its neck, is the small glass bulb *B*, containing iron filings, which can be made to oscillate and thus stir the liquid by means of a solenoid controlled through a commutator. *C* and *D* are glass bulbs containing the purified hydrogen cyanide and cyanogen chloride; they are provided with pressure stopcocks and standard taper joints for attachment to the filling manifold. The lead to the vacuum pump, McLeod gauge, and mercury manometer is shown at *F*; the manometer level was read on an etched glass scale ruled on the dividing engine in the Physics Department of this University, and checked by microscope comparator. The distillate receiver is the pycnometer bulb *G* of approximately 1 ml. capacity; a scale is etched on the capillary neck, and the volumes corresponding to the various scale divisions were determined by weight calibration with mercury according to the procedure of MacInnes, Cowperthwaite, and Huang (7). *A* and *G* are connected by the three-way stopcock *H*, either through the tube *K* of 5 mm. internal diameter, or through the tube *L*, which has a constriction in it 0.1 mm. in diameter.

In carrying out a measurement, roughly estimated amounts of the components in the flasks *C* and *D* were repeatedly outgassed by first freezing with liquid air, pumping off the residual gas, and then melting; this was continued until the residual air pressure after freezing was less than one micron as measured on the McLeod gauge. It is essential to remove air as completely as possible from the system since otherwise air will accumulate in *G* as the distillation proceeds, and the transport process through the capillary will be diffusion controlled. After outgassing, the flasks were removed from the manifold, allowed to come to temperature equilibrium, and weighed; blank experiments showed that loss in weight during the process of weighing was undetectable. The flasks were again attached to the manifold, the apparatus was evacuated (with tap *H* turned to tube *K*) and the contents of *C* and *D* were distilled into *A* with liquid air; as a rule the total charge thus introduced was from 15 to 25 gm. *C* and *D* were finally weighed empty, thus fixing the composition of the system gravimetrically.

The contents of *A* was once again thoroughly outgassed as described above; blank experiments in which the frozen sample was exposed to the Hyvac pump for one hour showed that the total loss in weight over this period was only 0.2 mgm. With stopcock *H* closed, the water-bath, which contained the whole apparatus to the right of the broken line in the figure, was filled and brought on temperature, stirrer *B* was started, and the vapour pressure of the liquid in *A* was read; the bath temperature was fixed by standard thermometers calibrated against the platinum resistance thermometer, which is temperature standard for this laboratory (4).

After reading the vapour pressure, the vapour in the lines was condensed back into *A* with liquid air, tap *M* was closed, the bath again brought on temperature, the stirrer started, and, when temperature equilibrium had been

reached, A was connected to G through L. Since G was outside the main thermostat in a small bath whose temperature was manually controlled, it was possible to carry on the distillation as slowly as desired; as a rule, the temperature of the small bath was initially about 3° C. below that of the main bath, but as the distillation proceeded it was found necessary to increase the temperature difference somewhat in order to maintain a roughly uniform rate of distillation. Normally the distillation of the 1 ml. of liquid which constituted the distillate required from one to one and a half hours, although in some runs the time was as great as three hours; in no case was there any evidence that the results depended on the rate of distillation, thus indicating that the conditions were not significantly different from those obtaining at equilibrium. When sufficient distillate had collected to fill G almost to the neck, tap H was closed, the vapour to the left of H was condensed into G with liquid air, tap N was closed, and G was detached from the apparatus with a blow torch at X, the resulting glass tip being broken off. The contents of G was just melted and vigorously shaken, and G was then placed in a glass sided water-bath whose temperature was maintained at 15° C. Owing to the expansion on warming, the level of the liquid rose into the capillary neck, where the exact level of the meniscus in relation to the etched scale could be read on the graticule in a telescope; since one scale division corresponded to approximately 0.005 ml., and since the level of the meniscus could easily be read to one-fiftieth of a scale division. the volume of the distillate could be determined with a precision of 0.01%. It should be added that once temperature equilibrium had been established in the bath, there was never any creep in the position of the meniscus, thus showing that the liquid in G was of uniform composition. The pycnometer was then removed from the bath, dried and weighed; tap N was opened, and the contents was allowed to evaporate in a fume hood. A final weighing then fixed the weight and consequently the density of the distillate. As a final check, the entire contents of the apparatus to the right of tap H was condensed at the end of the run into a small flask (not shown in the diagram) and weighed; as a rule, the weight so found plus that of the distillate agreed with the sum of the weights of the components initially introduced within 1 mgm.

The density–liquid-composition curve for the system was determined by distilling into mercury-calibrated pycnometer bulbs of approximately 1 ml. capacity first hydrogen cyanide and then cyanogen chloride, the weights distilled being determined by the loss in weight of small filling tubes as described above. Here the sum of the weights distilled agreed with the measured weight of the contents of the pycnometer within 0.02% or better.

The liquefied gases were supplied by the National Research Council. The hydrogen cyanide was fractionally distilled through phosphorus pentoxide five or six times, the first and last fractions being rejected each time. The vapour pressure of the purified material at 15° C. was 501.8 mm., which is moderate agreement with the value predicted by Giauque and Ruehrwein's vapour pressure equation, viz., 502.6 mm. (2). The equation previously

deduced by one of us (3) to represent Perry and Porter's vapour pressures (8) gives 503.2 mm. The cyanogen chloride was first distilled through phosphorus pentoxide and then fractionally crystallized repeatedly until its setting point became constant at $-6.90 \pm 0.02°$ C. in agreement with the findings of Winkler (12). Its vapour pressure at 15° C. was 833.0 mm. A plot of the vapour pressures reported by Klemenc and Wagner (6) indicates that this value is from 5 to 10 mm. above their curve; there is so much variation between their individual results, however, that any precise comparison is impossible. Whether the large discrepancy is due to difference in technique or is caused by different purity in the materials used is difficult to decide. It should be mentioned that different preparations of purified cyanogen chloride differed in their vapour pressures by not more than one- or two-tenth's of a millimetre; our value quoted above is an average.

Before the measurements discussed above can be interpreted, it is necessary to take account of the fact that in all the density measurements there was vapour above the liquid phase of slight but appreciable weight and of composition different from that of the liquid; the same is true for the vapour pressure determinations and for the calculation of the final composition of the liquid in bulb A; see reference (4). Accordingly, provisional density–liquid-composition, vapour-composition–liquid-composition, and vapour-pressure–liquid-composition curves were drawn ignoring this correction; the resulting correction both in weight and composition of the liquid concerned was then computed on the assumption that the vapour density of the vapour above a given liquid could be calculated by the gas laws from the provisional curves. The assumption of ideality is certainly untrue for hydrogen cyanide (see below) and is probably untrue for cyanogen chloride as well. However, owing to the relatively small vapour volumes involved (of the order of 0.4 cc. in the pycnometer measurements and of 40 cc. in the vapour pressure measurements) the error resulting from this assumption is entirely negligible. Calculation showed that a second calculation, using the corrected curves of liquid density, vapour pressure, and vapour composition was unnecessary. Finally, all weights were corrected to vacuum and all pressures to millimetres of mercury at 0° C. and sea level.

There is however a correction of an entirely different nature which must be noted. In an experiment, the initial composition and amount of the liquid phase are known, but the distillate analysed is an average sample since the compositions of both liquid and distillate change during the distillation. Thus if the fraction of the original system distilled be x, and the initial and final mole fractions of the liquid be N_0 and N_F, the measured average composition of the distillate $\overline{Y}$ will be given by

$$x\overline{Y} = N_0 - (1 - x)N_F . \qquad (1)$$

If Y stand for the true equilibrium vapour mole fraction corresponding to a liquid mole fraction N, then x, N_0, and N_F are connected by the well known relation

$$\ln (1 - x) = \int_{N_0}^{N_F} dN/(Y - N). \tag{2}$$

It is only when x is vanishingly small as in the measurements of Zawidzki (13) and of Roberts and Mayer (9) that the measured $\overline{Y}$ may be identified, as is often done, with either the true Y (N_0) or $Y(N_F)$. It is immediately evident that a somewhat better approximation will result from identifying $\overline{Y}$ with $Y(\overline{N})$, where $\overline{N}$ is defined by

$$(1 - x/2)\overline{N} = N_0 - x\overline{Y}/2 = (1 - x)N_F + x\overline{Y}/2. \tag{3}$$

$\overline{N}$ is thus the mean liquid composition if all the distillate had been of uniform composition $\overline{Y}$.

The question remains however as to the error introduced by this approximation. An estimate of this error, accurate enough except possibly in extreme cases, can be readily obtained from Equation (2) provided Y can be treated as sensibly linear in N over the range of x. In particular, if

$$Y = A + (B + 1)N. \tag{4}$$

Equation (2) can be integrated at once to give

$$A + BN_F = (A + BN_0)(1 - x)^B \tag{5}$$

Expansion of the right-hand side of (5) gives

$$N_F = N_0 - (A + BN_0)[x - (B - 1)x^2/2 + (B - 1)(B - 2)x^3/6..] \tag{6}$$

From (5) and (1) there results

$$\overline{Y} = A + (B + 1)N_0 - (A + BN_0)[(B + 1)x/2 - (B + 1)(B - 1)x^2/6..] \tag{7}$$

Combining (7) with (4) and (3) gives in turn

$$N(\overline{Y}) = N_0 - (A + BN_0)[x/2 - (B - 1)x^2/6 ..] \tag{8}$$

$$\overline{N} = N_0 - (A + BN_0)[x/2 - Bx^2/4 ..] \tag{9}$$

$$N(\overline{Y}) \approx \overline{N} - (A + BN_0)(B + 2)x^2/12 \tag{10}$$

$$\approx \overline{N} - (Y_0 - N_0)(dY/dN + 1)x^2/12. \tag{11}$$

In (11) $Y_0 - N_0$ and dY/dN may be replaced for purposes of approximation by $\overline{Y} - \overline{N}$ and $d\overline{Y}/d\overline{N}$; hence from a plot of $\overline{Y}$ versus $\overline{N}$ an estimate may be obtained at once of the correction which must be applied to Equation (3) to give the true equilibrium liquid composition corresponding to the measured (average) vapour composition. For most purposes this is all that is necessary, but in any event the resulting corrected $Y - N$ curve may be checked by tabular or graphical integration of Equation (2). In the experiments recorded here, x is at most 0.07, and since $\overline{Y} - \overline{N}$ and $d\overline{Y}/d\overline{N}$ are both relatively small, the second term in Equation (11) is at most 0.01 mole % and is consequently negligible.

Results

Table I gives the density results for the solutions; here N is the mole fraction of cyanogen chloride in the solution. A deviation plot from a quadratic in N gave densities for round values of the mole fraction, and from the resulting table, mole fractions could be obtained for experimentally determined values of G by interpolation using second differences. The vapour pressure measurements are summarized in Table II, and the equilibrium liquid–vapour compositions in Table III; in these N and Y refer to the liquid and vapour mole fractions of cyanogen chloride. For purposes of inter-

TABLE I

DENSITY OF CNCl–HCN SOLUTIONS AT 15° C. IN GM. PER ML.

x = weight fraction CNCl, N = mole fraction CNCl

x	0	0.1389	0.4082	0.4592	0.5258	0.6659
N	0	0.0662	0.2327	0.2718	0.3277	0.4670
G	0.6944	0.7380	0.8399	0.8622	0.8931	0.9658
x	0.7290	0.7957	0.8294	0.8746	0.9379	1.0000
N	0.5418	0.6313	0.6813	0.7541	0.8691	1.0000
G	1.0024	1.0440	1.0659	1.0967	1.1434	1.1920

TABLE II

VAPOUR PRESSURE OF CNCl–HCN SOLUTIONS AT 15° C.

N	0	0.0448	0.0777	0.1142	0.1261	0.1339	0.2483	0.2493
P, mm.	501.8	524.0	540.2	557.8	563.0	566.2	614.8	614.6
N	0.3293	0.4763	0.5586	0.7232	0.7793	0.8582	1.0000	
P, mm.	645.9	696.5	721.4	768.8	783.3	800.6	833.0	

TABLE III

VAPOUR–LIQUID EQUILIBRIUM FOR THE SYSTEM CNCl–HCN AT 15° C.

N	0.0761	0.1117	0.1317	0.2453	0.2459	0.3248
Y	0.1360	0.1926	0.2214	0.3677	0.3679	0.4535
N	0.4536	0.4727	0.5556	0.6293	0.7778	0.8571
Y	0.5801	0.5953	0.6633	0.7236	0.8347	0.8932

polation, deviation functions of the type discussed under Equation (1) of reference (5) were employed for the $Y - N$ data; the resulting deviation functions were at most 0.04 and consequently were suitable for graphical interpolation. In only four instances did the experimental points lie off the smooth curves as finally drawn by more than 0.05 mole % and in only two by more than 0.1 mole %, the discrepancy being approximately 0.2 mole % in both cases. The entries for round values of the liquid composition correspond to these deviation curves.

For the vapour pressures, a deviation plot of the type used by Scatchard and Raymond (10) was employed for values of N up to 0.5; for $N > 0.5$, the deviation from a linear function of N was plotted. In only four instances do the experimental points differ from the smooth curves drawn to represent the data by as much as 0.3 mm., and in the majority of cases by less than 0.2 mm. The entries in Table IV correspond to these curves.

TABLE IV

N	G	P, mm.	Y	N	G	P, mm.	Y
0	0.6944	501.8	0	0.40	0.9317	671.2	0.5295
0.025	0.7011	514.4	0.0470	0.50	0.9822	703.7	0.6195
0.05	0.7275	526.9	0.0920	0.60	1.0296	733.8	0.7005
0.10	0.7596	551.1	0.1750	0.70	1.0740	762.5	0.7775
0.15	0.7907	573.6	0.2470	0.80	1.1158	788.4	0.8510
0.20	0.8207	594.9	0.3125	0.90	1.1554	809.6	0.9250
0.30	0.8780	634.7	0.4290	1.00	1.1920	833.0	1.0000

A check on the self-consistency of our results by means of the Gibbs–Duhem equation is unfortunately not possible here owing to the uncertainty as to the equation of state for the vapour. Usherwood (11) and Felsing and Drake (1) have shown that hydrogen cyanide differs markedly from ideality through polymerization in the gaseous phase, and it would be surprising if cyanogen chloride did not show marked deviations as well. Nevertheless, the excellent reproducibility of the results indicates, we believe, that our measurements cannot be seriously in error.

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THE VAPOUR PRESSURE OF SOLUTIONS OF CARBON DIOXIDE IN DIFLUORODICHLOROMETHANE[1]

A. R. GORDON[2] AND E. A. MACWILLIAM[3]

Abstract

The vapour pressure of solutions of carbon dioxide in Freon has been determined at 10° and 20° C. for pressures up to 25 atm. At both temperatures, the vapour pressure is roughly linear in the mole fraction of carbon dioxide, the deviations being positive for solutions low in carbon dioxide and negative for solutions high in carbon dioxide; for a given concentration, the deviation becomes more negative the higher the temperature.

This research concerns the vapour pressure of the system carbon-dioxide–Freon (difluorodichloromethane) and was undertaken to provide data for possible uses of such chemically inert solutions.

Experimental

The experimental procedure consisted in condensing into a heavy glass bulb a sample of known composition and determining its vapour pressure by means of a closed-end mercury–air manometer. The apparatus is shown in Fig. 1. *A* is the bomb of Pyrex glass, capacity 12 cc. and wall thickness 3.5 mm.; it is contained in a water thermostat regulated to 0.005° C., bath temperatures being determined by means of a platinum resistance thermometer with National Bureau of Standards certificate. *A* is connected with the closed-end manometer *B*, which is contained in a glass-walled air thermostat regulated to 25.00 ± 0.05° C.; the height of the meniscus in *B* is read on a glass scale placed immediately behind the manometer. The dimensions of the manometer are such that at the highest pressures measured, viz., 25 atm., a movement of 0.05 mm. of the meniscus corresponds to a pressure change of 0.02 atm. The manometer was calibrated by determining the readings corresponding to the known vapour pressure of carefully dried ammonia, (5, p. 234) and sulphur dioxide (5, p. 236) over a range of temperatures. A large-scale deviation plot showed that the two sets were in agreement within the precision of the measurements, i.e., 0.01 atm. at the lower pressures to 0.02 atm. at the higher. The measured vapour pressures for Freon at 10°, 20°, and 30° C. agreed within the same limits with those reported by Gilkey, Gerard, and Bixler (3).

In Fig. 1, *C* is a glass bulb which serves as a gas reservoir (volume, determined by filling with water and weighing, 5.424 litres) and *D* is a mercury

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manometer that serves to determine the pressure in *C;* the mercury level in *D* was read on a plate glass scale similar to those used in this laboratory (see reference (4)). The dotted line in the figure indicates a second air thermostat held at 25.00 ± 0.05° C.; taps 1 and 2 are enclosed in a small copper box in this thermostat so that they can be manipulated without disturbing the temperature of bulb *C*.

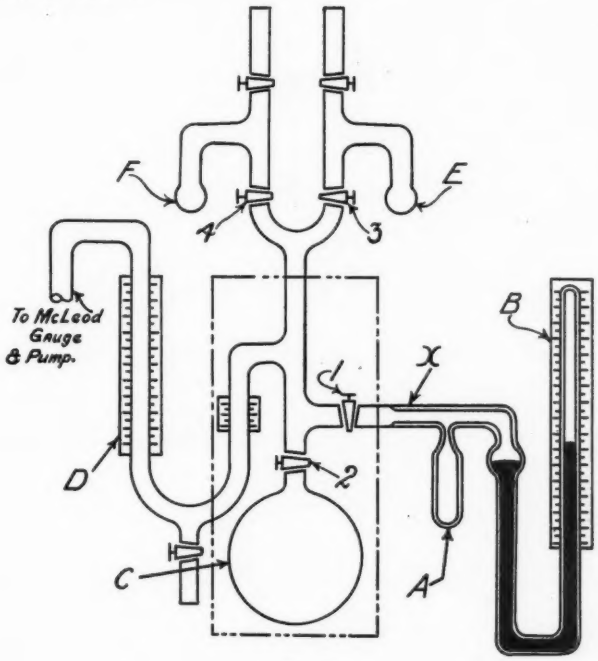

FIG. 1

Freon and carbon dioxide, after being dried by passage over Anhydrone, were condensed under vacuum with liquid air in the small side tubes *E* and *F;* the Freon was allowed to melt and boil to remove traces of dissolved air, and was then frozen again. The whole apparatus was evacuated, and the reading corresponding to vacuum on manometer *D* was taken. Tube *F* was then allowed to warm and carbon dioxide was allowed to pass into the apparatus with tap 1 closed until the pressure had attained the desired value; tap 4 was then closed and the carbon dioxide in *F* was again frozen with liquid air. After *C* had come to temperature equilibrium, the pressure was read on *D*, a suitable amount of carbon dioxide was condensed into *A* through tap 1 with liquid air, and the final pressure in the apparatus to the left of tap 1 was read. From the two pressure readings, the known volume of *C* and of the lines, and the equation of state, it was then possible to compute the number of moles of carbon dioxide frozen in *A*. The apparatus was next evacuated, and the procedure

repeated with the Freon in tube *E*. With *A* still immersed in liquid air, the heavy glass capillary lead was next sealed off at *x*, and the water-bath filled and brought on temperature. To hasten attainment of equilibrium, the contents of *A* was stirred by a glass plunger with soft iron core, actuated by an electromagnet surrounding *A*. In all cases the final temperature was approached both from the side of higher and of lower values, and it was only when the two pressure readings agreed within the precision of the measurements that temperature equilibrium was assumed to be attained. To compute the composition of the system from the pressure readings, the equation of state of Beattie and Bridgeman was employed for carbon dioxide (1) and that of Buffington and Gilkey for Freon (2).

It should be noted that the composition obtained as described is that of the system as a whole and not that of the condensed phase; see reference (4). It is possible, however, by a short series of approximations to make a moderately accurate correction for this by assuming that the composition of the vapour in equilibrium with the condensed phase is given by Raoult's law, since the volume of the vapour above the liquid—approximately 3 cc.—is known from the dimensions of the apparatus and the volume of the liquid phase. With from 0.07 to 0.10 moles of Freon and from 0.005 to 0.075 moles carbon dioxide in the system, the correction varied from 0.3 mole % for the runs weakest in carbon dioxide to slightly over 1% for those richest in carbon dioxide. We believe that the corrected liquid compositions are probably accurate to 0.1 mole % or better.

Results

Table I gives for 10° and for 20° C. the observed vapour pressures in atmospheres as a function of the liquid mole fraction of the carbon dioxide; the

TABLE I

10° C.			20° C.		
N_{CO_2}	P, atm.	δ, atm.	N_{CO_2}	P, atm.	δ, atm.
0	4.17	0	0	5.59	0
0.0466	6.25	+0.20	0.0460	7.98	+0.05
0.1041	8.94	+0.58	0.1037	11.19	+0.32
0.2078	13.25	+0.71	0.2068	16.24	+0.12
0.2496	14.70	+0.49	0.2474	17.87	−0.32
0.3277	17.26	−0.10	0.3252	20.79	−1.35
0.4079	20.04	−0.54	0.4063	24.43	−1.85
0.5403	24.98	−0.93	—	—	—

deviation function δ, recorded in the third column of the table and plotted in Fig. 2, is defined by

$$P = P_F^\circ + N_{CO_2}(P_{CO_2}^\circ - P_F^\circ) + \delta \qquad (1)$$

where P_F° and $P_{CO_2}^\circ$ are the vapour pressures of Freon and carbon dioxide at the temperature in question; thus if the vapour were a perfect gaseous

solution, the liquid obeyed Raoult's law, and the thermodynamic potentials of both components in the liquid were independent of pressure, δ would be identically zero. It is apparent from Fig. 2 that the deviations from Raoult's

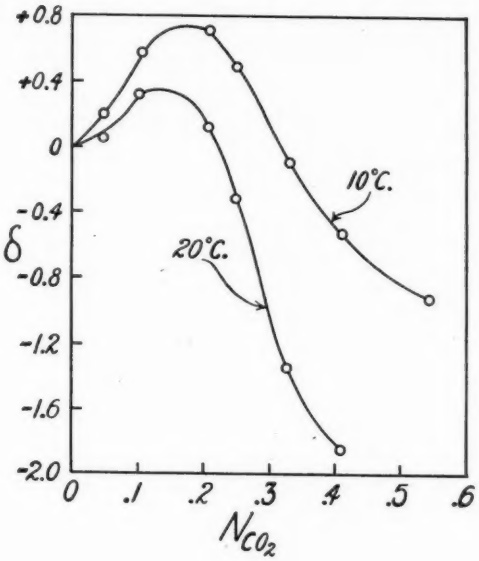

FIG. 2.

law cannot be serious, thus providing some justification for the method discussed above of computing the liquid composition from that of the system. It should be noted that the deviations are positive at the lower carbon dioxide concentrations and negative at the higher, and that for a given concentration the deviation becomes more negative with rising temperature.

Table II gives the vapour pressure for round values of the liquid composition and also the temperature coefficient $\triangle \log P/\triangle (1/T)$; these latter quantities may be used to obtain rough estimates of the vapour pressures at higher temperatures. An idea of how much reliance may be placed on such an

TABLE II

N_{CO_2}	$P_{10°}$	$P_{20°}$	$\Delta \log P/\Delta(1/T)$	N_{CO_2}	$P_{10°}$	$P_{20°}$	$\Delta \log P/\Delta(1/T)$
0	4.17	5.59	−1055	0.35	18.00	21.86	−700
0.05	6.44	8.24	890	0.40	19.74	24.15	725
0.10	8.74	10.99	825	0.45	21.59	—	—
0.15	10.91	13.55	780	0.50	23.45	—	—
0.20	12.94	15.92	745	0.55	25.35	—	—
0.25	14.74	17.94	710	1.00	44.41	56.50	−860
0.30	16.36	19.79	−685	—	—	—	—

extrapolation may be obtained from Table III, which gives the results of a few measurements carried out at 30° C. The first two lines give the liquid mole fraction of carbon dioxide and the observed vapour pressure at 30° C.;

TABLE III

N_{CO_2}	0	0.0454	0.2063	0.2462	0.3216
$P_{30°}$, obs.	7.34	10.08	19.79	21.62	25.06
$P_{10°}$	4.17	6.22	13.19	14.60	17.05
$\Delta \log P/\Delta(1/T)$	−1055	−900	−740	−710	−690
$P_{30°}$, calc.	7.35	10.08	19.62	21.38	24.68

the third and fourth lines the corresponding vapour pressures at 10° C. (obtained from the plot of Fig. 2) and the temperature coefficients, and the last line the value at 30° C. computed from that for 10° C. and the temperature coefficient. It is apparent that for solutions low in carbon dioxide, the extrapolation gives reliable results, but that for solutions high in carbon dioxide it can give little more than an order of magnitude. On the other hand, since this method gives results that are too low, and the assumption that Raoult's law is obeyed gives results that are on the whole too high, the two used in conjunction should fix rough limits for the vapour pressures at higher temperatures.

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ACETYLATION AND BENZOYLATION OF DIBASIC SUGAR ACIDS[1]

By M. Adelman[2] and J. G. Breckenridge[3]

Abstract

Fully acetylated mucic acid, D-glucosaccharic anhydride, D-mannosaccharic anhydride, and α-D-glucopentahydroxypimelic acid have been prepared by the action of acetyl chloride on the neutral zinc salts of the corresponding acids. Fully benzoylated mucic, D-glucosaccharic, and D-mannosaccharic acids have been prepared in a similar manner. The action of acyl or aroyl halides on the neutral zinc salts of the dibasic sugar acids is proposed as a general method for preparation of the fully substituted derivatives.

The preparation of fully acylated or aroylated dibasic sugar acids has not been extensively investigated, and no generally applicable method for the preparation of such compounds has been reported. The only fully acetylated dibasic acids described to date are diacetyl-D-tartaric acid (1, 2, 3, 11) tetra-acetyl mucic acid (7, 9, 13), and tetra-acetyl allomucic acid (4). Dibenzoyl-D-tartaric acid (10) is the only fully benzoylated compound of this type recorded. No fully acetylated or benzoylated derivatives have been prepared from acids normally existing as lactones. A method has been developed recently for the preparation of fully acetylated aldonic acids by the acetylation of the aldonamide with acetic anhydride and zinc chloride (12), or by the acetylation of the cadmium aldonate with acetic anhydride and dry hydrogen chloride (8).

In the course of another investigation it was necessary to prepare fully acetylated α-D-glucopentahydroxypimelic acid, and a method was developed using acetyl chloride and the neutral zinc salt of the dibasic acid. The product was obtained in good yield, and it was thought that the method might be extended to the preparation of similar derivatives. In order to test the generality of the procedure, the acids chosen for experiment were (i) mucic acid, existing normally as the free acid, (ii) D-glucosaccharic acid, existing as the monolactone, and (iii) D-mannosaccharic acid, existing as the dilactone. The action of acetyl chloride on the neutral zinc salts of these acids resulted in the formation of the fully acetylated acid or acid anhydride, and the use of benzoyl chloride under similar conditions gave the fully benzoylated derivatives, with varying amounts of tribenzoylated derivatives as additional products. The results obtained would seem to indicate that a general method is available for the preparation of this type of compound.

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Contribution from the Department of Chemical Engineering, University of Toronto, Toronto, Ont. Condensed from a portion of a thesis submitted in partial fulfilment of requirements for the degree Ph.D.

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[3] *Associate Professor of Chemical Engineering.*

Experimental

Zinc mucate.—A filtered solution of zinc acetate dihydrate (28 gm., 0.128 mole) in 250 ml. water was added to a boiling solution of mucic acid (25 gm., 0.119 mole) in 1500 ml. water. The resulting white crystalline precipitate (together with a second crop obtained by concentrating the mother liquor) weighed 35.4 gm. (91%). Found: ZnO, 24.7%. Calc. for $C_6H_8O_8Zn \cdot 3H_2O$: ZnO, 24.9%.

Zinc D-glucosaccharate.—A filtered solution of zinc acetate dihydrate (11.5 gm., 0.052 mole) was added to a solution of 10 gm. (0.05 mole) of D-glucosaccharolactone (m.p. 103° to 108° C.) in 1 litre water. The mixture was digested on the steam-bath for three hours, and the white crystalline product formed (together with a second crop) weighed 14.1 gm. (99%). Found: ZnO, 26.9%. Calc. for $C_6H_8O_8Zn \cdot 1.5\ H_2O$: ZnO, 27.1%.

Zinc D-mannosaccharate.—This was prepared from D-mannosaccharodilactone, obtained from D-mannitol by the method of Easterfield (5), and from D-mannose by the method of Haworth, Heslop, Salt, and Smith (6). A filtered solution of 7.9 gm. (0.036 mole) zinc acetate dihydrate in 250 ml. water was added to 5.0 gm. (0.035 mole) of the dilactone dissolved in 250 ml. water. The solution was concentrated *in vacuo* at 35° to 40° C. to 250 ml., made up to 400 ml. with distilled water, and allowed to stand at room temperature. Crystals began to deposit within 24 hr., and after standing for a week, 6.0 gm. (80%) of the crystalline zinc salt was obtained. Found: ZnO, 25.1%. Calc. for $C_6H_8O_8Zn \cdot 3H_2O$: ZnO, 24.9%.

Zinc α-D-glucopentahydroxypimelate.—Calcium α-D-glucopentahydroxypimelate (25 gm., 0.09 mole) was suspended in 250 ml. water, and 12 ml. concentrated nitric acid (0.095 equiv.) was added with stirring until the suspended salt had all dissolved. Zinc carbonate (15 gm., 0.12 mole) was then added to the solution, the mixture heated to gentle boiling, and digested for an hour. The mixture was then filtered hot, the filtrate decolorized with Norit, concentrated to 100 ml. *in vacuo*, and an equal volume of ethanol added. The precipitate was washed with 80% ethanol, and weighed 23.2 gm. (85%). Found: ZnC, 26.3%. Calc. for $C_7H_{10}O_9Zn$: ZnO, 26.8%. The salt precipitates as the hydrate ($1.5\ H_2O$), but was dehydrated before analysis.

Tetra-acetyl mucic acid.—A suspension of 1.2 gm. oven-dried zinc mucate in 5 ml. acetyl chloride was refluxed at 60° C. for 1.5 hr. The acetyl chloride remaining was distilled off *in vacuo* and ice–water added to the residue. A pale yellow crystalline solid was obtained, which after drying at 105° C. for several hours weighed 1.2 gm. (93%), and had a melting point of 238° C.* One recrystallization from 95% ethanol raised the melting point to 243° C. (Recorded in literature, m.p. 243° C.)

Tetra-acetyl D-glucosaccharic anhydride.—Zinc D-glucosaccharate hemihydrate (2.4 gm., 0.0085 mole) was weighed into a flask. Acetyl chloride (5 ml., 0.07 mole) was added through a reflux condenser, and, after the reaction

* *Melting points are corrected.*

subsided, the mixture was refluxed at 60° C. for an hour. The excess acetyl chloride was removed *in vacuo*, and the remaining viscous oil treated with 25 ml. chloroform. The chloroform solution, after being washed with dilute hydrochloric acid and water, and dried over sodium sulphate, was concentrated to half volume, and on the addition of petroleum ether a white crystalline product was obtained in about 35% yield. A recrystallization from ethyl-acetate–petroleum-ether gave a product with a melting point of 178° to 178.5° C., $[\alpha]_D^{22}$ + 149.7° (c = 0.77 in dry acetone). Found*: C, 46.57, 46.51; H, 4.45, 4.32%. Calc. for $C_{14}H_{16}O_{11}$: C, 46.57; H, 4.48%.

Tetra-acetyl D-mannosaccharic anhydride.—Prepared in the same manner as the previous compound, yield 37.5%, m.p. 177° to 178° C., $[\alpha]_D^{22}$ + 244° (c = 1.07 in dry acetone). Found: C, 46.40, 46.67; H, 4.37, 4.39%. Calc. for $C_{14}H_{16}O_{11}$: C, 46.57; H, 4.48%.

α-D-glucopenta-acetoxypimelic acid.—Prepared in a similar manner. The washed and dried chloroform extract on concentrating to dryness *in vacuo* yielded a sandy-coloured resin. This could not be crystallized, but on standing in contact with water for several days a 70% yield of white crystals was obtained. After recrystallization from ethyl-acetate–petroleum-ether the melting point was 122° C. Found: C, 44.98, 45.02; H, 5.03, 5.07%. Calc. for $C_{17}H_{22}O_{14}$: C, 45.33; H, 4.92%.

Tetrabenzoyl mucic acid.—Oven-dried zinc mucate (5.0 gm., 0.017 mole) was mixed with 12 ml. (0.104 mole) of benzoyl chloride in a flask, and heated under a reflux condenser on the water-bath. A reaction began at 45° C. and hydrogen chloride was evolved. The mixture was maintained at 45° C. until reaction had ceased and the material in the flask was solid. This was then broken up, and washed with dilute hydrochloric acid and water. The product was crystallized from 100 ml. 95% ethanol, and a second crop obtained on concentration of the mother liquor. The combined crops were washed several times with cold benzene and dried. Yield, 4.1 gm. (39%), m.p. 198° to 198.5° C. Recrystallization from benzene did not alter the melting point. Found: C, 65.50, 65.57; H, 4.30, 4.28%. Calc. for $C_{34}H_{26}O_{12}$: C, 65.17; H, 4.18%.

Tetrabenzoyl D-glucosaccharic acid.—Zinc D-glucosaccharate hemihydrate (1.0 gm., 0.004 mole) was mixed with 2.4 ml. (0.022 mole) of benzoyl chloride and warmed on a water-bath under a reflux condenser. The reaction began at 80° C., and the mixture was held at that temperature for an hour. The product was isolated and purified as for the mucic acid derivative. Yield, 0.8 gm. (36%). After several recrystallizations from ethyl-acetate–petroleum-ether the compound had a melting point of 173° C., $[\alpha]_D^{22}$ + 102.7° (c = 0.80 in dry acetone). Found: C, 65.16, 65.18; H, 4.28, 4.26%. Calc. for $C_{34}H_{26}O_{12}$: C, 65.17, H, 4.18%.

Tetrabenzoyl D-mannosaccharic acid.—Reaction was carried out in the same manner as the previous experiment. Only a portion of the reaction product

* *Carbon–hydrogen microanalyses by A. E. Ledingham and Mrs. E. Mason.*

would dissolve in hot 95% ethanol, and the ethanol-insoluble material was thoroughly washed with hot ethanol and recrystallized several times from ethyl-acetate–petroleum-ether. Yield 24%, m.p. 186° to 187° C., $[\alpha]_D^{22}$ + 267° (c = 0.55 in dry acetone). Found: C, 64.74, 65.31; H, 4.20, 4.24%. Calc. for $C_{34}H_{26}O_{12}$: C, 65.17; H. 4.18%.

Tribenzoyl D-mannosaccharolactone.—The ethanol solution from the previous experiment was decolorized with Norit and concentrated to 15 ml. The fine, needle-like crystals were washed with 90% ethanol and dried at 90° C. Yield, 1.1 gm. (66%). After recrystallization from ethyl-acetate–petroleum-ether the melting point was 196° C., and $[\alpha]_D^{22}$ + 245° (c = 1.07 in dry acetone). No mutarotation was observed after 96 hr. Found: C, 64.27, 64.60; H, 3.97, 4.00%. Calc. for $C_{27}H_{20}O_{10}$: C, 64.23; H, 3.97%.

Acknowledgment

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STUDY ON THE SYNTHESIS OF VALINE BY THE STRECKER METHOD[1]

By Roger Gaudry[2]

Abstract

A systematic investigation of the synthesis of *dl*-valine by the Strecker method, starting from isobutyraldehyde, has been made. The potassium-cyanide–ammonium-chloride procedure, as modified by us, has been found to be the most convenient for the large scale laboratory preparation of this amino acid, considering the over-all yield, the purity of the amino acid, and the time required, as well as the ease of preparation. A continuous ether extraction of the amino nitrile has been introduced. This accounts for the high yield and easy separation of the pure amino acid.

Introduction

The principle of the Strecker method (8) for the synthesis of amino acids has been known for nearly a century. Although it has been applied by many investigators to the synthesis of about 10 naturally occurring amino acids, the method, despite various improvements, does not seem to be widely used for the large scale preparation of amino acids, except perhaps for alanine, glycine, and possibly serine.

Now that many aldehydes are commercially available, it seems worth while to investigate further the method and the various improvements that have been suggested, and to try to ascertain whether the method can be modified so as to give better yields than those usually reported.

The most careful studies made of the Strecker method are those of Cocker and Lapworth (3) and Bucherer and collaborators (1, 2). Important also are the syntheses by the Strecker method published in *Organic Syntheses* (7). But it is indeed remarkable that these authors have worked mainly with ketones as starting material, and rarely with aldehydes, which might have led to naturally occurring amino acids.

The study of the synthesis of valine was considered desirable because of the high cost of the commercial synthetic product, the low cost of isobutyraldehyde as starting material, and the fact that there is no known practicable procedure for the isolation of the natural form of valine from protein hydrolysates.

Valine was synthesized from isobutyraldehyde by Lipp in 1880 (4), from hydrocyanic acid and ammonia, but the yield is not reported. No further

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work on the subject appears to have been published. The synthesis of valine from isobutyraldehyde has been investigated by us as follows:

(1) Using alkali cyanides and ammonium chloride.

(2) Using free hydrocyanic acid and ammonia.

(3) Via the bisulphite addition compound.

(4) Via the corresponding hydantoin.

Part I

The Synthesis of *dl*-Valine from Potassium Cyanide and Ammonium Chloride

Cocker and Lapworth have recommended (3) the exclusion of even small amounts of alkali metals in the synthesis of the more soluble amino acids by the Strecker method. We have found on the contrary that *dl*-valine, which is a very soluble amino acid, can be satisfactorily synthesized from potassium cyanide and ammonium chloride, provided the amino nitrile is extracted from the aqueous solution before being hydrolysed. A continuous ether extractor is very convenient, since it allows for the complete extraction, with a comparatively small volume of ether, of an amino nitrile which is not contaminated by alkali metals.

After the synthesis had been carried out under various experimental conditions, it was found that:

1. Only freshly distilled isobutyraldehyde should be used. The commercial aldehyde employed as received gave much lower yields.
2. The reaction between the aldehyde and the cyanide and ammonium salt is best carried out at room temperature. Some cooling is recommended while the aldehyde is added to the mixture of cyanide and ammonium salt, to avoid overheating, but no further cooling is necessary.
3. An excess of potassium cyanide and ammonium chloride does not increase the yield. But the presence of an excess of ammonia in the reaction mixture significantly increases the yield. The presence of a little ether is also beneficial.
4. If the amino nitrile is extracted by shaking with several successive portions of ether, instead of using a continuous ether extractor, the overall yield of crude valine is about 10% lower.
5. Hydrolysis of the amino nitrile with hydrochloric acid is to be recommended. This acid gives as good a yield as sulphuric acid. It enables easier separation of the amino acid from the reaction mixture, and also avoids the precipitation, as barium sulphate, of the large excess of sulphuric acid necessary for the hydrolysis.
6. The amino acid can be isolated by the glacial acetic acid method described by Marvel (6), but the isolation is more easily and rapidly effected by dissolving the *dl*-valine hydrochloride in absolute ethyl alcohol,

filtering the insoluble salts, and precipitating the valine with a slight excess of pyridine.

By following in detail the experimental conditions described below, a 65% over-all yield of nearly pure valine, or a 62.5% yield of very pure valine, is obtained.

EXPERIMENTAL

dl-Valine

A mixture of ammonium chloride (60 gm., 1.1 mole), potassium cyanide (66 gm., 1.0 mole), water (400 ml.), and concentrated ammonium hydroxide (155 ml.) is placed in a one litre, three-necked flask half immersed in cold running water and fitted with a separatory funnel, mechanical stirrer, and a long stem thermometer dipping into the liquid. The mixture is stirred and freshly distilled isobutyraldehyde (91 ml., 1.0 mole) is added drop by drop. The addition of the aldehyde requires about half an hour, in the course of which the temperature of the reaction mixture reaches about 40° C., but rapidly decreases to room temperature when the addition of the aldehyde is complete. Ethyl ether (100 ml.) is then added, and the mixture is continuously stirred for about six hours. After it has stood overnight, the reaction mixture is poured into a continuous ether extractor and extracted with ether (250 ml.) for 48 hr. The ether is then evaporated *in vacuo* at room temperature, and the residual pale yellow liquid is treated with concentrated hydrochloric acid (500 ml.). The mixture is shaken, allowed to stand at room temperature overnight, and boiled under reflux for 24 hr. It is then evaporated to dryness *in vacuo* on the water-bath, water (300 ml.) is added, and the solution is boiled under reflux with charcoal for half an hour, filtered, and again evaporated to dryness *in vacuo*. The solid residue is taken up with absolute ethyl alcohol (500 ml.) and boiled under reflux for a few minutes, and the solution is cooled, filtered from insoluble ammonium chloride, and pyridine (100 ml.) is added. The solution is well shaken and allowed to stand overnight in the ice-box. The precipitated *dl*-valine is filtered on a Büchner funnel, washed with successive (25 ml.) portions of absolute ethyl alcohol until free from pyridine, and allowed to dry. The yield of perfectly white, nearly pure valine is 76.3 gm., 65%. The amino acid is dissolved in boiling water (490 ml.), and 95% alcohol (500 ml.) is added, and the mixture is left overnight in the ice-box. The amino acid is filtered, washed with 95% alcohol, and dried. Yield, 63.2 gm. The filtrate is evaporated, the residue is dissolved in boiling water (55 ml.), and 95% alcohol (60 ml.) added; on cooling, a second crop of 8.7 gm. separates. A third crop of 1.3 gm. may be obtained by working up the residues. Total yield, 73.2 gm., 62.5%. The recovery in the crystallization is 96%. The very pure amino acid obtained in this way contains the theoretical amount of nitrogen. Found (Kjeldahl): N, 12.00%. Calc. for $C_5H_{11}O_2N$: N, 11.96%. It melts in a sealed tube at 289° to 290° C.*

* *Melting points are not corrected.*

Part II

The Synthesis of *dl*-Valine from Hydrocyanic Acid and Ammonia

In their study of the Strecker method for the synthesis of amino acids, Cocker and Lapworth (3), who used an excess of hydrocyanic acid and ammonia, claimed an average yield of about 70% of amino acids, but they did not prepare *dl*-valine, although they made *dl*-norvaline in a 68% yield.

We have prepared *dl*-valine from isobutyraldehyde, using an aqueous solution of hydrocyanic acid and concentrated ammonia. Our results indicate that an excess of ammonia is essential to obtain a good yield of amino acid, but that an excess of hydrocyanic acid does not increase the yield. Using two moles of hydrocyanic acid and two moles of ammonia per mole of aldehyde, a 40% yield of *dl*-valine is obtained. With two moles of hydrocyanic acid and four moles of ammonia, the yield is 44.5%. But with one mole of hydrocyanic acid and four moles of ammonia, a 58.5% yield of *dl*-valine is obtained.

It is remarkable that the best yield obtained with free hydrocyanic acid is from 10 to 12% lower than the yield claimed for similar compounds by Cocker and Lapworth, and about 7% lower than the best yield obtained in the synthesis of *dl*-valine from potassium cyanide, ammonium chloride, and ammonia.

EXPERIMENTAL

dl-Valine

Isobutyraldehyde (91 ml., 1 mole) is added dropwise to a cooled mechanically stirred solution containing hydrocyanic acid (27 gm., 1 mole), concentrated ammonia (270 ml., 4 moles), and water (100 ml.). After 12 hr. of stirring at room temperature, the mixture is extracted with ether for 24 hr. in a continuous ether extractor, the ether is evaporated *in vacuo*, and the residue is hydrolysed by boiling under reflux for 24 hr. with concentrated hydrochloric acid (500 ml.). The valine is isolated as described in Part I. Yield, 68.4 gm., 58.5%.

Part III

The Synthesis of *dl*-Valine Via the Bisulphite Addition Compound

We have investigated the preparation of *dl*-valine by the reaction of isobutyraldehyde with sodium acid sulphite and potassium cyanide. The main reason for this was to ascertain whether, by using an excess of sodium acid sulphite and potassium cyanide, the yield of cyanhydrin and that of *dl*-valine could be increased.

Using 1.5 moles of sodium acid sulphite and 1.5 moles of potassium cyanide per mole of aldehyde, a 46% yield of *dl*-valine is obtained, while, using one mole of acid sulphite and one mole of cyanide per mole of aldehyde, the yield is increased to 53.5%.

EXPERIMENTAL

dl-Valine

Isobutyraldehyde (91 ml., 1 mole) is added dropwise to a cooled and mechanically stirred solution of sodium acid sulphite (105 gm., 1 mole) in water (100 ml.). A solution of potassium cyanide (66 gm., 1 mole) in water (100 ml.) is then added slowly to the cooled and stirred paste of bisulphite addition compound, and stirring is continued for one hour at room temperature. The mixture is extracted with ether for 24 hr. in a continuous ether extractor, the ether is evaporated *in vacuo*, and the resulting free cyanhydrin is added dropwise to mechanically stirred, concentrated ammonia (270 ml., 4 moles). After six hours of stirring at room temperature, the mixture is extracted with ether for 24 hr. in a continuous ether extractor, the ether is evaporated *in vacuo*, and the resulting amino nitrile is hydrolysed by boiling under reflux for 24 hr. with concentrated hydrochloric acid (500 ml.). The valine is isolated as described in Part I. Yield, 62.5 gm., 53.5%.

Part IV

The Synthesis of *dl*-Valine Via the 5-Isopropylhydantoin

Bucherer and collaborators (1) have claimed that they could obtain very high yields of hydantoins, usually from 80 to 90%, by allowing an aldehyde or a ketone bisulphite compound to react with a large excess of potassium cyanide and ammonium carbonate in 50% alcohol. We have not been able to obtain similar results with isobutyraldehyde. The reason probably is that 5-isopropylhydantoin is difficult to separate from the large amount of potassium carbonate formed as a by-product of the reaction. And it must be kept in mind that Bucherer worked only with ketones, or with aldehydes containing an aromatic nucleus, therefore his hydantoins were much less soluble in water than 5-isopropylhydantoin.

We have prepared the hydantoin by using a method that does not require the separation of the hydantoin from alkali salts. It consists in preparing the free cyanhydrin in the manner described in Part III, and allowing it to react with an excess of ammonium carbonate. Pure 5-isopropylhydantoin is obtained in a 77% yield.

This preparation of 5-isopropylhydantoin is interesting in so far as the hydantoin can be hydrolysed to *dl*-valine with a very high yield, for an 85% yield for the hydrolysis would mean an over-all yield of 65%, which we had already achieved by the method described in Part I.

The acid hydrolysis of hydantoins usually gives poor yields because the hydantoin ring is more readily closed than opened in the presence of acids. However, a 63% yield of valine was obtained by boiling under reflux 5-isopropylhydantoin for 60 hr. with 20% hydrochloric acid. But the hydantoin is readily hydrolysed in an 85% yield by refluxing at atmospheric pressure with barium hydroxide, although we have not been able to achieve anything like the 95% yield claimed by Livak *et al.* (5) by hydrolysis, under pressure, of 5-(β-methylmercaptoethyl)hydantoin with barium hydroxide.

EXPERIMENTAL

5-Isopropylhydantoin

The cyanhydrin is first prepared in the manner described in Part III, starting with one mole (91 ml.) of isobutyraldehyde. After it has been extracted from the reaction mixture the cyanhydrin is added to a solution of ammonium carbonate (230 gm., 2.4 moles) in water (400 ml.), and the mixture is kept at 50° C. for five hours. After being heated at 95° to 100° C. for one hour to remove the excess of ammonium carbonate, the solution is filtered hot and concentrated to a small volume. On cooling, 5-isopropylhydantoin separates in long needles. Crude yield of yellow-coloured hydantoin: 119 gm., 84%. After two crystallizations from hot water, including treatment with Norite, the yield is: 109 gm., 77%; m.p. 142° to 143° C. After many recrystallizations: m.p. 144° to 145° C. Found (Kjeldahl): N, 19.4%. Calc. for $C_6H_{10}O_2N_2$: N, 19.7%.

dl-Valine

In a 500 ml. round bottomed flask are placed 5-isopropylhydantoin (14.2 gm., 0.1 mole), barium hydroxide (80 gm. of the octahydrate, 0.25 mole), water (100 ml.) and the mixture is boiled under reflux for 24 hr., the top of the condenser being fitted with a soda-lime tube. Carbon dioxide is then passed into the mixture until no more precipitate forms. The solution is filtered hot, the precipitate is washed with hot water, and the filtrate is evaporated to dryness *in vacuo*. The residue is *dl*-valine, which is recrystallized in the usual way. Yield, 9.8, gm., 85%.

Conclusion

These results seem to indicate that the reaction of cyanhydrin formation is not an equilibrium reaction, since an excess of nitrile is not beneficial, while the reaction between the aldehyde or the cyanhydrin with ammonia is definitely an equilibrium reaction, for an excess of ammonia gives a much better yield. Furthermore, the best method for the large scale laboratory preparation of *dl*-valine is probably the Strecker method as modified by us, using potassium cyanide, ammonium chloride, ammonia, and a continuous ether extractor for the isolation of the amino nitrile. Following a typical run starting with five moles (360 gm.) of isobutyraldehyde, more than 350 gm. of very pure, recrystallized valine was obtained. About the same over-all yield is obtained if the synthesis is made by way of the hydantoin, followed by hydrolysis with barium hydroxide, but this procedure requires more time and manipulation, and the required number of recrystallizations of the product is one more than that necessary when the first procedure is used.

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